AMENDMENTS TO THE CLAIMS

Listing of Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Currently amended) A method for treating a patient suffering from one or more insulin related ailments selected from the group consisting of hyperglycemia, hypoglycemia, diabetes mellitus, insulinomas, insulin and hypoglycemic drug overdose, gastric dumping syndrome and congenital hyperinsulinism, Alzheimer's disease, which method comprises the step of: administering to a patient in need thereof a therapeutically effective amount of a non-peptidyl compound ~~that is a biological modulator of insulin activity~~, which ~~compound~~ possesses one or more ionic and hydrophobic chemical moieties spatially located so as to mimic the spatial location of at least an ionic or a hydrophobic amino acid residue of insulin, wherein said compound is an insulin agonist ~~which amino acids are associated with the binding of insulin to its receptor~~.

2. (Currently amended) A method according to claim 1, wherein the ionic amino acid residue is selected from the group ~~comprising~~ consisting of: A21 Asn, B21 Glu and A17 Glu.

3. (Original) A method according to claim 1, wherein the ionic and hydrophobic amino acid residue(s) is(are) selected from the group consisting of: A21 Asn, B21 Glu, A17 Glu, B24 Phe, B25 Phe, A19 Tyr, B12 Val, B16 Tyr, A2 Ile, A3 Val and A1 Gly.

4. (Currently amended) A method according to claim 1, wherein at least one amino acid is selected from the group ~~comprising~~ consisting of: A17 Glu, B21 Glu and A21 Asn; and at least one amino acid is selected from the group consisting of: B24 Phe, B25 Phe, A19 Tyr, B12 Val and B1~~2~~6 Tyr.

5. (Previously amended) A method according to claim 1, wherein the non-peptidyl compound possesses ionic and hydrophobic chemical moieties spatially located so as to mimic ionic and hydrophobic residues associated with at least one of the following groups of amino acid residues:

(i.) A21 Asn, B21 Glu, A17 Glu, B24 Phe, B25 Phe;

(ii.) A21 Asn, B21 Glu, B24 Phe, B25 Phe;

(iii.) A21 Asn, B21 Glu, B24 Phe, B25 Phe, A1 Gly, A2 Ile, A3 Val;

(iv.) A21 Asn, B21 Glu, A17 Glu, A19 Tyr, A1 Gly, A2 Ile, A3 Val;

(v.) A21 Asn, B21 Glu, A17 Glu, B12 Val, A1 Gly, A2 Ile, A3 Val;

(vi.) A21 Asn, B21 Glu, B12 Val, A1 Gly, A2 Ile, A3 Val;

(vii.) A21 Asn, B21 Glu, A17 Glu, B16 Tyr, A1 Gly, A2 Ile, A3 Val;

(viii) A21 Asn, B21 Glu, A17 Glu, A19 Tyr, B12 Val, B16 Tyr;

(ix.) A21 Asn, B21 Glu, A19 Tyr, B12 Val, B16 Tyr;

(x.) A21 Asn, B21 Glu, A17 Glu, B24 Phe, B25 Phe, A19 Tyr, B12 Val, B16 Tyr;

(xi.) A21 Asn, B21 Glu, B24 Phe, B25 Phe, A19 Tyr, B12 Val, B16 Tyr;

(xii) A21 Asn, B21 Glu, B24 Phe, B25 Phe, B12 Val, B16 Tyr;

(xiii.) A21 Asn, B21 Glu, A17 Glu, B24 Phe, B25 Phe, A19 Tyr;

(xiv.) A21 Asn, B21 Glu, B24 Phe, B25 Phe, A19 Tyr;

(xv.) A21 Asn, A17 Glu, B24 Phe, B25 Phe, A19 Tyr;

(xvi.) B21 Glu, A17 Glu, B24 Phe, B25 Phe, A19 Tyr;

(xvii.) A21 Asn, B21 Glu, A17 Glu, B24 Phe, B25 Phe, B12 Val;

(xviii.) A21 Asn, B21 Glu, B24 Phe, B25 Phe, B12 Val;

(xix.) A21 Asn, A17 Glu, B24 Phe, B25 Phe, B12 Val;

(xx.) B21 Glu, A17 Glu, B24 Phe, B25 Phe, B12 Val;

(xxi.) A21 Asn, B21 Glu, A17 Glu, B24 Phe, B25 Phe, B16 Tyr;

(xxii.) A21 Asn, B21 Glu, B24 Phe, B25 Phe, B16 Tyr;

(xxiii.) A21 Asn, A17 Glu, B24 Phe, B25 Phe, B16 Tyr;

(xxiv.) B21 Glu, A17 Glu, B24 Phe, B25 Phe, B16 Tyr;

(xxv.) A21 Asn, B21 Glu, A17 Glu, B24 Phe, A19 Tyr, B12 Val, B16 Tyr;

(xxvi.) A21 Asn, B21 Glu, B24 Phe, A19 Tyr, B12 Val, B16 Tyr;

(xxvii.)A21 Asn, A17 Glu, B24 Phe, A19 Tyr, B12 Val, B16 Tyr;

(xxviii.) B21 Glu, A17 Glu, B24 Phe, A19 Tyr, B12 Val, B16 Tyr;

(xxix.) A21 Asn, B21 Glu, A17 Glu, B25 Phe, A19 Tyr, B12 Val, B16 Tyr;

(xxx.) A21 Asn, B21 Glu, B25 Phe, A19 Tyr, B12 Val, B16 Tyr;

(xxxi.) A21 Asn, A17 Glu, B25 Phe, A19 Tyr, B12 Val, B16 Tyr; or

(xxxii.) B21 Glu, A17 Glu, B25 Phe, A19 Tyr, B12 Val.

6. (Currently amended) A method according to claim 1, wherein the non-peptidyl compound has the following formula:

$AXYXZ_n$ (formula 1)

where A is W or VXW;

V is V_1 or V_2;

V is substituted with up to two X groups;

V_1 is a phenyl or 6 membered heteroaromatic ring, optionally substituted with up to 5 R_1 groups;

V_2 is a 5 member ring system which may incorporate up to 4 hetero atoms which may be independently a nitrogen atom, a nitrogen atom optionally substituted with R_2, oxygen or sulfur, the ring system being optionally substituted with up to 4 R_1 groups;

W is W_1 or W_2 or W_3;

W is substituted with up to two X groups;

W_1 is V_1;

W_2 is a fused bicyclic ring system comprising rings of 5 or 6 atoms, which may incorporate up to 4 hetero atoms, which may be independently a nitrogen atom, a nitrogen atom optionally substituted with R_2, oxygen or sulfur, the system being optionally substituted with up to seven R_1 groups;

W_3 is $-N(R_2)R'_2$;

R_1 is independently H, OH, alkyl, alkenyl, alkynyl, alkoxy, alkanol, hydroxyalkoxy, haloalkyl, haloalkoxy, halogen, SH, thioalkyl, cyano (-CN), $N(R_2)R'_2$, phenyl, phenyl optionally substituted with up to five alkyl groups of 1 to 3 carbon atoms or up to five halogen atoms, benzyl, phenethyl, nitro, $-COR_3$, $-R_5COR_3$, $-R_5SOR_3$, $-R_5SO_2R_3$, $-SO_2N(R_2)R'_2$ or azido;

R_2 and R'_2 are independently H, alkyl of 1 to 6 carbon atoms, alkenyl of 3 to 6 carbon atoms, alkynyl of 3 to 6 carbons, hydroxyalkyl of 2 to 6 carbons, alkoxy of 2 to 6 carbons, haloalkyl, haloalkenyl, haloalkoxy, benzyl, benzyl optionally substituted with up to four R_1 groups, phenylethyl, phenylethyl optionally substituted with up to four R_1 groups, arylalkyl, and where R_2 and R'_2 can also be joined to form cyclic structures;

R_3 is independently H, OH, alkyl, alkenyl, alkynyl, alkoxy, alkanol, hydroxyalkoxy, $-R_4N(R_2)R'_2$, mesyl, triflouromesyl, $-NHSO_2CH_3$ or $-NHSO_2CF_3$;

R_4 is independently a bond, alkyl, alkenyl or alkynyl;

X is independently, a bond, $-R_4N(R_2)R_4-$, $-R_4N{=}NR_4-$, $-R_4N(R_2)-N(R_2)R_4-$, $-R_4OR_4-$, $-R_4SR_4-$, $-R_5-$, $-R_5O-$, $-R_5S-$, $-R_5N(R_2)-$, -SO-, sulfonyl ($-SO_2-$), -CO-, -CONH-, -NHCONH-, -NHCO-, -CONHCO-, $-CON(R_2)-$, $-R_5COR_5-$, $-R_5COR_5N(R_2)R_5-$, $-N(R_2)CO-$ or $-R_4N(R_2)R_4COR_4-$;

R_5 is independently alkyl, alkenyl, alkynyl, alkoxy, alkanol, hydroxyalkoxy;

Y is either Y_1, Y_2 or Y_3;

Y is substituted with at least two, but optionally up to four X linking groups;

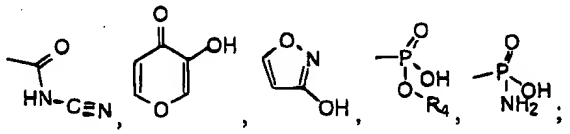
Y_1 is a fused bicyclic ring system comprising rings of 5 or 6 atoms which may incorporate up to 4 hetero atoms, which may be independently a nitrogen atom, a nitrogen atom optionally substituted with R_2, oxygen or sulfur; the ring system optionally independently incorporating a sulfoxide (SO), sulfone (SO_2) or carbonyl (CO) group and optionally up to seven R_1 groups;

Y_2 is a 6:6:6 or a 6:5:6 fused tricyclic system which may incorporate up to 4 hetero atoms which may be independently a nitrogen atom, a nitrogen atom optionally substituted with R_2, oxygen or sulfur, the ring system optionally independently incorporating a sulfoxide (SO), sulfone (SO_2) or carbonyl (CO) group, and the ring system being substituted with at least two, but optionally up to four X linking groups and optionally up to seven R_1 groups;

Y_3 is V_1;

Z is independently $-R_6COOH$, $-R_6SO_3H$, $-R_6NO_2$, $-R_6SO_2H$, $-R_6SO_2NHR_2$; $-R_7SO_2NHCOR_4$ -N-trifluoromesylsulfonamidate, -OH, -2-yl-hydroxyethanoic acid (-CH(OH)COOH), -3-yl-2-hydroxypropanoic acid ($-CH_2CH(OH)COOH$) -2-yl-2-

hydroxypropanoic acid (-CH(CH$_3$)(OH)COOH), -3-yl-2,3-dihydroxypropanoic acid (-CH(OH)CH(OH)COOH), -2-yl-2,3-dihydroxypropanoic acid (-C(CH$_2$(OH))(OH)COOH), -3-yl-2-hydroxypropan-3-one-1-oic acid (-COCH(OH)COOH, 2-yl-2-hydroxypropandioic acid (-C(COOH)(OH)COOH), -2-yl-propandioic acid (-C(COOH)(H)COOH), -4-yl-2-hydroxybutan-4-one-1-oic acid (-COCH$_2$CH(OH)COOH, 2-yl-2-hydroxybutan-1,4-dioic acid (-C(OH)(COOH)CH$_2$COOH), 3-yl-2-hydroxybutan-1,4-dioic acid (-CH(CH(OH)COOH)COOH), 5-yl-tetrazole,



R$_6$ is independently a bond, alkyl, alkenyl, alkynyl, alkoxy, -CO(CH$_2$)$_n$-, where n is an integer between 0 and 4, alkanoic, alkenoic or alkynoic;

with the exception that where W_1 is an optionally substituted phenyl then Y_{+2} cannot be an optionally substituted phenyl.

7. (Original) A method according to claim 6, wherein the non-peptidyl compound is a dimer or heterodimer wherein the compounds are joined through a X linking group by way of their V or W groups.

8. (Original) A method according to claim 6, wherein when V is V_1 or V_2, then:

V_1 is selected from the group consisting of, benzene, pyridine, pyridazine, pyrimidine, pyrazine or triazine and is optionally substituted with up to 5 R_1 groups; and

V_2 is selected from the group consisting of, cyclopenta-1,3-diene, pyrrole, furan, thiophene, oxazole, isoxazole, pyrazole, imidazole, thiazole, isothiazole or triazole and is optionally substituted with up to 4 R_1 groups;

and W is W_2 then

W_2 is selected from the group consisting of naphthalene, quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, indole, benzothiophene, benzofuran, benzimidazole, indazole, benzoxazole, benzisooxazole,

benzthiazole, benzisothiazole, purine, indoline or isoindoline and is optionally substituted with up to seven R_1 groups;

and Y is either Y_1 or Y_2 then

Y_1 is selected from the group consisting of croman, isochroman, benzofuran, cromene, 1,2,3,4-tetrahydronaphthalene, 1,4-dihydronaphthalene, indan, indene, benzopiperidine, indoline, isoindoline, quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline or pteridine, coumarin or 2,3-dihydrocoumarin and is optionally substituted with up to seven R_1 groups; and

Y_2 is selected from the group consisting of 9H-xanthone, 9H-xanthene, phenoxathiin, phenoxathiin-10-oxide, phenoxathiin-10-dioxide, acridine, phenazine, phenothiazine, phenoxazine, phenothiazine-5-oxide, phenothiazine-5-dioxide, thiathrene-5-dioxide, thiathrene-5-oxide, carbazole, dibenzo[b,d]furan or dibenzo[b,d]thiophene and is optionally substituted with up to seven R_1 groups.

9. (Original) A method according to claim 6, wherein when A is VXW then:V is phenyl or pyrazole, optionally substituted with up to 5 R_1 groups;and when A is W or VXW then W is W_1, W_2 or W_3 wherein W_1 is phenyl optionally substituted with up to 5 R_1 groups;

W_2 is naphthalene or quinoline optionally substituted with up to seven R_1 groups wherein R_1 is independently H, OH, methyl, ethyl, propyl, nitro, methoxy, ethoxy, 2-hydroxyethoxy, chloro, fluoro or acetyl;

W_3 is $-N(R_2)R_2$ wherein R_2 is propyl; X is independently, a bond, methoxy ($-OCH_2$), oxypropoxy ($-O(CH_2)_3O-$), hexenyloxy ($-O(CH_2)_4CH=CH-$), sulfonyloxy ($-SO_2O-$), methyl ($-CH_2-$), amidyl (-CONH-) or -NHCONH-; and Y is either Y_1 or Y_2 then Y_1 is croman, 4-H-chromen-4-one or napthalene optionally substituted with up to seven R_1 groups wherein R_1 is independently H, OH, methyl, ethyl, propyl, nitro, methoxy, ethoxy, 2-hydroxyethoxy, chloro, fluoro or acetyl;

Y_2 is 9H-xanthone optionally substituted with up to seven R_1 groups wherein R_1 is independently H, OH, methyl, ethyl, propyl, nitro, methoxy, ethoxy, 2-hydroxyethoxy, chloro, fluoro or acetyl;

Y_3 is phenyl optionally substituted with up to 5 R_1 groups wherein R_1 is independently H, OH, methyl, ethyl, propyl, nitro, methoxy, ethoxy, 2-hydroxyethoxy, chloro, fluoro or acetyl; and

Z is independently $-R_6COOH$, $-R_6SO_3H$ or -N-trifluoromesylsulfonamidate wherein R_6 is independently a bond or propyl.

10. (Original) A method according to claim 6, wherein the non-peptidyl compound is selected from the following group of compounds:

(i.) 4,4'-Methylenebis[3-hydroxy-2-naphthalenecarboxylic acid];

(ii.) 7-[3-(4-acetyl-2-ethyl-5-hydroxyphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

(iii.) 2,4-dichloro-6-(*N*-(trifluoromethanesulfonyl))sulfamoylphenyl 3,5-dichloro-2-hydroxybenzenesulfonate;

(iv.) 7-[(4-acetyl-3-hydroxy-2-propylphenyl)methoxy]-4-oxo-8-propyl-4*H*-1-benzopyran-2-carboxylic acid;

(v.) 7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2*H*-1-benzopyran-2-carboxylic acid;

(vi.) 3,4-dihydro-8-propyl-7-[[3-[2-ethyl-5-hydroxy-4-(1*H*-pyrazol-3-yl)phenoxy]propyl]oxy]-2*H*-1-benzopyran-2-carboxylic acid;

(vii.) 3,4-dihydro-8-propyl-7-[[3-[2-ethyl-5-hydroxy-4-ethoxyphenoxy]propyl]oxy]-2*H*-1-benzopyran-2-carboxylic acid;

(viii.) 3-[4-[7-carboxy-9-oxo-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-9*H*-xanthene]]propanoic acid;

(ix.) 8-propyl-7-(quinol-2'-ylmethoxy)-3,4-dihydro-2*H*-1-benzopyran-2-carboxylic acid;

(x.) 7-(naphth-2'-ylmethoxy)-8-propyl-3,4-dihydro-2*H*-1-benzopyran-2-carboxylic acid; (xi.) *N*-(trifluoromethanesulfonyl)-3,5-dinitro-4-(*N'*,*N'*-dipropylamino)benzenesulfonamide;

(xii.) 8-propyl-7-[3-[4-(4-fluorophenyl)-2-ethyl-5-hydroxyphenoxy]propoxy]-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid;

(xiii.) 3,4-dihydro-7-[[6-(4-methoxyphenyl)hexenyl]oxy]-8-propyl-2H-1-benzopyran-2-carboxylic acid; or

(xiv.) 8,8'-[Carbonylbis[imino-3,1-phenylenecarbonylimino(4-methyl-3,1-phenylene)carbonylimino]]bis-1,3,5-naphthalenetrisulfonic acid.

11. (Canceled)

12. (Canceled)

13. (Canceled)

14. (Canceled)

15. (Canceled)

16. (Currently amended) A method for identifying a non-peptidyl compound possessing ionic and hydrophobic chemical moieties spatially located so as to mimic particular ionic and hydrophobic amino acid residues of insulin ~~which are associated with the binding of insulin to its receptor~~, said method comprising the steps of: (1) comparing the three dimensional structure of the non-peptidyl compound with a three dimensional pharmacophore of an active site of insulin; and (2) selecting a non-peptidyl compound with ionic and hydrophobic chemical moieties spatially located so as to mimic said site.

17. (Original) A method for determining whether a non-peptidyl compound identified according to the method of claim 16 is an agonist or an antagonist, said method comprising the step of: exposing the compound to an insulin or insulin like receptor and measuring the change in biological activity following exposure of the compound to the receptor.

18. (Cancelled)

19. (Cancelled)

20. (Amended) A method according to claim 6 wherein V_1 is selected from the group consisting of: benzene, pyridine, pyridazine, pyrimidine, pyrazine, triazine.

21. (Amended) A method according to claim 6 wherein V_2 is selected from the group consisting of: cyclopenta-1,3-diene, pyrrole, furan, thiophene, oxazole, isoxazole, pyrazole, imidazole, thiazole, isothiazole or triazole, optionally substituted with up to 4 R_1 groups.

22. (Amended) A method according to claim 6 wherein W_2 is selected from the group consisting of: naphthalene, quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, indole, benzothiophene, benzofuran, benzimidazole, indazole, benzoxazole, benzisooxazole, benzthiazole, benzisothiazole, purine, indoline, isoindoline. improper markush

23. (Amended) A method according to claim 6 wherein R_2 and R'_2 are joined to form cyclic structures selected from the group consisting of : pyrrolidine, piperidine, hexahydro-1H-azepine, morpholine or piperazine.

24. (Amended) A method according to claim 6 wherein Y_1 is selected from the group consisting of: croman, isochroman, benzofuran, cromene, 1,2,3,4-tetrahydronaphthalene, 1,4-dihydronaphthalene, indan, indene, benzopiperidine, indoline, isoindoline, quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline or pteridine, coumarin or 2,3-dihydrocoumarin.

25. (Amended) A method according to claim 6 wherein Y_2 is selected from the group consisting of: 9H-xanthone, 9H-xanthene, phenoxathiin, phenoxathiin-10-oxide, phenoxathiin-10-dioxide, acridine, phenazine, phenothiazine, phenoxazine, phenothiazine-5-oxide, phenothiazine-5-dioxide, thiathrene-5-dioxide, thiathrene-5-oxide, carbazole, dibenzo[b,d]furan, dibenzo[b,d]thiophene. improper markush

26. (Cancelled)

27. (Cancelled)

28. (Cancelled)

29. (Cancelled)

30. (Cancelled)

31. (Cancelled)

32. (New) A method for treating a patient suffering from one or more insulin related ailments selected from the group consisting of hyperglycemia, hypoglycemia, diabetes mellitus, insulinomas, insulin and hypoglycemic drug overdose, gastric dumping syndrome and congenital hyperinsulinism, Alzheimer's disease, which method comprises the step of: administering to a patient in need thereof a therapeutically effective amount of a non-peptidyl compound which possesses one or more ionic and hydrophobic chemical moieties spatially located so as to mimic the spatial location of at least an ionic or a hydrophobic amino acid residue of insulin, wherein said compound is an insulin antagonist.

33. (New) A method according to claim 32, wherein the ionic amino acid residue is selected from the group consisting of: A21 Asn, B21 Glu and A17 Glu.

34. (New) A method according to claim 32, wherein the ionic and hydrophobic amino acid residue(s) is(are) selected from the group consisting of: A21 Asn, B21 Glu, A17 Glu, B24 Phe, B25 Phe, A19 Tyr, B12 Val, B16 Tyr, A2 Ile, A3 Val and A1 Gly.

35. (New) A method according to claim 32, wherein at least one amino acid is selected from the group consisting of: A17 Glu, B21 Glu and A21 Asn; and at least one amino acid is selected from the group consisting of: B24 Phe, B25 Phe, A19 Tyr, B12 Val and B16 Tyr.

36. (New) A method according to claim 32, wherein the non-peptidyl compound possesses ionic and hydrophobic chemical moieties spatially located so as to mimic ionic and hydrophobic residues associated with at least one of the following groups of amino acid residues:

(i.) A21 Asn, B21 Glu, A17 Glu, B24 Phe, B25 Phe;

(ii.) A21 Asn, B21 Glu, B24 Phe, B25 Phe;

(iii.) A21 Asn, B21 Glu, B24 Phe, B25 Phe, A1 Gly, A2 Ile, A3 Val;

(iv.) A21 Asn, B21 Glu, A17 Glu, A19 Tyr, A1 Gly, A2 Ile, A3 Val;

(v.) A21 Asn, B21 Glu, A17 Glu, B12 Val, A1 Gly, A2 Ile, A3 Val;

(vi.) A21 Asn, B21 Glu, B12 Val, A1 Gly, A2 Ile, A3 Val;

(vii.) A21 Asn, B21 Glu, A17 Glu, B16 Tyr, A1 Gly, A2 Ile, A3 Val;

(viii) A21 Asn, B21 Glu, A17 Glu, A19 Tyr, B12 Val, B16 Tyr;

(ix.) A21 Asn, B21 Glu, A19 Tyr, B12 Val, B16 Tyr;

(x.) A21 Asn, B21 Glu, A17 Glu, B24 Phe, B25 Phe, A19 Tyr, B12 Val, B16 Tyr;

(xi.) A21 Asn, B21 Glu, B24 Phe, B25 Phe, A19 Tyr, B12 Val, B16 Tyr;

(xii) A21 Asn, B21 Glu, B24 Phe, B25 Phe, B12 Val, B16 Tyr;

(xiii.) A21 Asn, B21 Glu, A17 Glu, B24 Phe, B25 Phe, A19 Tyr;

(xiv.) A21 Asn, B21 Glu, B24 Phe, B25 Phe, A19 Tyr;

(xv.) A21 Asn, A17 Glu, B24 Phe, B25 Phe, A19 Tyr;

(xvi.) B21 Glu, A17 Glu, B24 Phe, B25 Phe, A19 Tyr;

(xvii.) A21 Asn, B21 Glu, A17 Glu, B24 Phe, B25 Phe, B12 Val;

(xviii.) A21 Asn, B21 Glu, B24 Phe, B25 Phe, B12 Val;

(xix.) A21 Asn, A17 Glu, B24 Phe, B25 Phe, B12 Val;

(xx.) B21 Glu, A17 Glu, B24 Phe, B25 Phe, B12 Val;

(xxi.) A21 Asn, B21 Glu, A17 Glu, B24 Phe, B25 Phe, B16 Tyr;

(xxii.) A21 Asn, B21 Glu, B24 Phe, B25 Phe, B16 Tyr;

(xxiii.) A21 Asn, A17 Glu, B24 Phe, B25 Phe, B16 Tyr;

(xxiv.) B21 Glu, A17 Glu, B24 Phe, B25 Phe, B16 Tyr;

(xxv.) A21 Asn, B21 Glu, A17 Glu, B24 Phe, A19 Tyr, B12 Val, B16 Tyr;

(xxvi.) A21 Asn, B21 Glu, B24 Phe, A19 Tyr, B12 Val, B16 Tyr;

(xxvii.)A21 Asn, A17 Glu, B24 Phe, A19 Tyr, B12 Val, B16 Tyr;

(xxviii.) B21 Glu, A17 Glu, B24 Phe, A19 Tyr, B12 Val, B16 Tyr;

(xxix.) A21 Asn, B21 Glu, A17 Glu, B25 Phe, A19 Tyr, B12 Val, B16 Tyr;

(xxx.) A21 Asn, B21 Glu, B25 Phe, A19 Tyr, B12 Val, B16 Tyr;

(xxxi.) A21 Asn, A17 Glu, B25 Phe, A19 Tyr, B12 Val, B16 Tyr; or

(xxxii.) B21 Glu, A17 Glu, B25 Phe, A19 Tyr, B12 Val.

37. (New) A method according to claim 32, wherein the non-peptidyl compound has the following formula:

$AXYXZ_n$ (formula 1)

where A is W or VXW;

V is V_1 or V_2;

V is substituted with up to two X groups;

V_1 is a phenyl or 6 membered heteroaromatic ring, optionally substituted with up to 5 R_1 groups;

V_2 is a 5 member ring system which may incorporate up to 4 hetero atoms which may be independently a nitrogen atom, a nitrogen atom optionally substituted with R_2, oxygen or sulfur, the ring system being optionally substituted with up to 4 R_1 groups;

W is W_1 or W_2 or W_3;

W is substituted with up to two X groups;

W_1 is V_1;

W_2 is a fused bicyclic ring system comprising rings of 5 or 6 atoms, which may incorporate up to 4 hetero atoms, which may be independently a nitrogen atom, a nitrogen atom optionally substituted with R_2, oxygen or sulfur, the system being optionally substituted with up to seven R_1 groups;

W_3 is $-N(R_2)R'_2$;

R_1 is independently H, OH, alkyl, alkenyl, alkynyl, alkoxy, alkanol, hydroxyalkoxy, haloalkyl, haloalkoxy, halogen, SH, thioalkyl, cyano (-CN), $N(R_2)R'_2$, phenyl, phenyl optionally substituted with up to five alkyl groups of 1 to 3 carbon atoms or up to five halogen atoms, benzyl, phenethyl, nitro, $-COR_3$, $-R_5COR_3$, $-R_5SOR_3$, $-R_5SO_2R_3$, $-SO_2N(R_2)R'_2$ or azido;

R_2 and R'_2 are independently H, alkyl of 1 to 6 carbon atoms, alkenyl of 3 to 6 carbon atoms, alkynyl of 3 to 6 carbons, hydroxyalkyl of 2 to 6 carbons, alkoxy of 2 to 6 carbons, haloalkyl, haloalkenyl, haloalkoxy, benzyl, benzyl optionally substituted with up to four R_1 groups, phenylethyl, phenylethyl optionally substituted with up to four R_1 groups, arylalkyl, and where R_2 and R'_2 can also be joined to form cyclic structures;

R_3 is independently H, OH, alkyl, alkenyl, alkynyl, alkoxy, alkanol, hydroxyalkoxy, $-R_4N(R_2)R'_2$, mesyl, triflouromesyl, $-NHSO_2CH_3$ or $-NHSO_2CF_3$;

R_4 is independently a bond, alkyl, alkenyl or alkynyl;

X is independently, a bond, $-R_4N(R_2)R_4-$, $-R_4N{=}NR_4-$, $-R_4N(R_2)-N(R_2)R_4-$, $-R_4OR_4-$, $-R_4SR_4-$, $-R_5-$, $-R_5O-$, $-R_5S-$, $-R_5N(R_2)-$, -SO-, sulfonyl ($-SO_2-$), -CO-, -CONH-, -NHCONH-, -NHCO-, -CONHCO-, $-CON(R_2)-$, $-R_5COR_5-$, $-R_5COR_5N(R_2)R_5-$, $-N(R_2)CO-$ or $-R_4N(R_2)R_4COR_4-$;

R_5 is independently alkyl, alkenyl, alkynyl, alkoxy, alkanol, hydroxyalkoxy;

Y is either Y_1, Y_2 or Y_3;

Y is substituted with at least two, but optionally up to four X linking groups;

Y_1 is a fused bicyclic ring system comprising rings of 5 or 6 atoms which may incorporate up to 4 hetero atoms, which may be independently a nitrogen atom, a nitrogen atom optionally substituted with R_2, oxygen or sulfur, the ring system optionally independently incorporating a sulfoxide (SO), sulfone (SO_2) or carbonyl (CO) group and optionally up to seven R_1 groups;

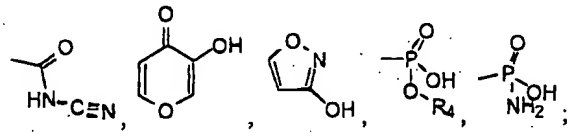
Y_2 is a 6:6:6 or a 6:5:6 fused tricyclic system which may incorporate up to 4 hetero atoms which may be independently a nitrogen atom, a nitrogen atom optionally substituted with R_2, oxygen or sulfur, the ring system optionally independently incorporating a sulfoxide (SO), sulfone (SO_2) or carbonyl (CO) group, and the ring system being substituted with at least two, but optionally up to four X linking groups and optionally up to seven R_1 groups;

Y_3 is Y_1;

Z is independently $-R_6COOH$, $-R_6SO_3H$, $-R_6NO_2$, $-R_6SO_2H$, $-R_6SO_2NHR_2$; $-R_7SO_2NHCOR_4$ -N-trifluoromesylsulfonamidate, -OH, -2-yl-hydroxyethanoic acid (-CH(OH)COOH), -3-yl-2-hydroxypropanoic acid ($-CH_2CH(OH)COOH$) -2-yl-2-hydroxypropanoic acid ($-CH(CH_3)(OH)COOH$), -3-yl-2,3-dihydroxypropanoic acid (-CH(OH)CH(OH)COOH), -2-yl-2,3-dihydroxypropanoic acid ($-C(CH_2(OH))(OH)COOH$), -3-yl-2-hydroxypropan-3-one-1-oic acid (-COCH(OH)COOH, 2-yl-2-hydroxypropandioic acid (-C(COOH)(OH)COOH), -2-yl-propandioic acid (-C(COOH)(H)COOH), -4-yl-2-hydroxybutan-4-onc-1-oic acid ($-COCH_2CH(OH)COOH$, 2-yl-2-hydroxybutan-1,4-dioic acid

(-C(OH)(COOH)CH_2COOH), 3-yl-2-hydroxybutan-1,4-dioic acid

(-CH(CH(OH)COOH)COOH), 5-yl-tetrazole,



R_6 is independently a bond, alkyl, alkenyl, alkynyl, alkoxy, -$CO(CH_2)_n$-, where n is an integer between 0 and 4, alkanoic, alkenoic or alkynoic;

with the exception that where W_1 is an optionally substituted phenyl then Y_3 cannot be an optionally substituted phenyl.

38. (New) A method according to claim 37, wherein the non-peptidyl compound is a dimer or heterodimer wherein the compounds are joined through a X linking group by way of their V or W groups.

39. (New) A method according to claim 37, wherein when V is V_1 or V_2, then:

V_1 is selected from the group consisting of, benzene, pyridine, pyridazine, pyrimidine, pyrazine or triazine and is optionally substituted with up to 5 R_1 groups; and

V_2 is selected from the group consisting of, cyclopenta-1,3-diene, pyrrole, furan, thiophene, oxazole, isoxazole, pyrazole, imidazole, thiazole, isothiazole or triazole and is optionally substituted with up to 4 R_1 groups;

and W is W_2 then

W_2 is selected from the group consisting of naphthalene, quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, indole, benzothiophene, benzofuran, benzimidazole, indazole, benzoxazole, benzisooxazole, benzthiazole, benzisothiazole, purine, indoline or isoindoline and is optionally substituted with up to seven R_1 groups; and Y is either Y_1 or Y_2 then

Y_1 is selected from the group consisting of croman, isochroman, benzofuran, cromene, 1,2,3,4-tetrahydronaphthalene, 1,4-dihydronaphthalene, indan, indene, benzopiperidine, indoline, isoindoline, quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline or pteridine, coumarin or 2,3-dihydrocoumarin and is optionally substituted with up to seven R_1 groups; and

Y_2 is selected from the group consisting of 9H-xanthone, 9H-xanthene, phenoxathiin, phenoxathiin-10-oxide, phenoxathiin-10-dioxide, acridine, phenazine, phenothiazine, phenoxazine, phenothiazine-5-oxide, phenothiazine-5-dioxide, thiathrene-5-dioxide, thiathrene-5-oxide, carbazole, dibenzo[b,d]furan or dibenzo[b,d]thiophene and is optionally substituted with up to seven R_1 groups.

40. (New) A method according to claim 37, wherein when A is VXW then:

V is phenyl or pyrazole, optionally substituted with up to 5 R_1 groups;

and when A is W or VXW then W is W_1, W_2 or W_3 wherein

W_1 is phenyl optionally substituted with up to 5 R_1 groups;

W_2 is naphthalene or quinoline optionally substituted with up to seven R_1 groups wherein R_1 is independently H, OH, methyl, ethyl, propyl, nitro, methoxy, ethoxy, 2-hydroxyethoxy, chloro, fluoro or acetyl;

W_3 is $-N(R_2)R_2$ wherein R_2 is propyl;

X is independently, a bond, methoxy ($-OCH_2-$), oxypropoxy ($-O(CH_2)_3O-$), hexenyloxy ($-O(CH_2)_4CH=CH-$), sulfonyloxy ($-SO_2O-$), methyl ($-CH_2-$), amidyl (-CONH-) or -NHCONH-; and Y is either Y_1 or Y_2 then

Y_1 is croman, 4-H-chromen-4-one or napthalene optionally substituted with up to seven R_1 groups wherein R_1 is independently H, OH, methyl, ethyl, propyl, nitro, methoxy, ethoxy, 2-hydroxyethoxy, chloro, fluoro or acetyl;

Y_2 is 9H-xanthone optionally substituted with up to seven R_1 groups wherein R_1 is independently H, OH, methyl, ethyl, propyl, nitro, methoxy, ethoxy, 2-hydroxyethoxy, chloro, fluoro or acetyl;

Y_3 is phenyl optionally substituted with up to 5 R_1 groups wherein R_1 is independently H, OH, methyl, ethyl, propyl, nitro, methoxy, ethoxy, 2-hydroxyethoxy, chloro, fluoro or acetyl; and

Z is independently $-R_6COOH$, $-R_6SO_3H$ or -N-trifluoromesylsulfonamidate wherein R_6 is independently a bond or propyl.

41. (New) A method according to claim 37, wherein the non-peptidyl compound is selected from the following group of compounds:

(i.) 4,4'-Methylenebis[3-hydroxy-2-naphthalenecarboxylic acid];

(ii.) 7-[3-(4-acetyl-2-ethyl-5-hydroxyphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

(iii.) 2,4-dichloro-6-(*N*-(trifluoromethanesulfonyl))sulfamoylphenyl 3,5-dichloro-2-hydroxybenzenesulfonate;

(iv.) 7-[(4-acetyl-3-hydroxy-2-propylphenyl)methoxy]-4-oxo-8-propyl-4*H*-1-benzopyran-2-carboxylic acid;

(v.) 7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2*H*-1-benzopyran-2-carboxylic acid;

(vi.) 3,4-dihydro-8-propyl-7-[[3-[2-ethyl-5-hydroxy-4-(1*H*-pyrazol-3-yl)phenoxy]propyl]oxy]-2*H*-1-benzopyran-2-carboxylic acid;

(vii.) 3,4-dihydro-8-propyl-7-[[3-[2-ethyl-5-hydroxy-4-ethoxyphenoxy]propyl]oxy]-2*H*-1-benzopyran-2-carboxylic acid;

(viii.) 3-[4-[7-carboxy-9-oxo-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-9*H*-xanthene]]propanoic acid;

(ix.) 8-propyl-7-(quinol-2'-ylmethoxy)-3,4-dihydro-2*H*-1-benzopyran-2-carboxylic acid;

(x.) 7-(naphth-2'-ylmethoxy)-8-propyl-3,4-dihydro-2*H*-1-benzopyran-2-carboxylic acid;

(xi.) *N*-(trifluoromethanesulfonyl)-3,5-dinitro-4-(*N*',*N*'-dipropylamino)benzenesulfonamide;

(xii.) 8-propyl-7-[3-[4-(4-fluorophenyl)-2-ethyl-5-hydroxyphenoxy]propoxy]-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid;

(xiii.) 3,4-dihydro-7-[[6-(4-methoxyphenyl)hexenyl]oxy]-8-propyl-2H-1-benzopyran-2-carboxylic acid; or

(xiv.) 8,8'-[Carbonylbis[imino-3,1-phenylenecarbonylimino(4-methyl-3,1-phenylene)carbonylimino]]bis-1,3,5-naphthalenetrisulfonic acid.

42. (New) A method according to claim 37 wherein V_1 is selected from the group consisting of: benzene, pyridine, pyridazine, pyrimidine, pyrazine, triazine.

consisting of: cyclopenta-1,3-diene, pyrrole, furan, thiophene, oxazole, isoxazole, pyrazole, imidazole, thiazole, isothiazole or triazole, optionally substituted with up to 4 R_1 groups.

44. (New) A method according to claim 37 wherein W_2 is selected from the group consisting of: naphthalene, quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, indole, benzothiophene, benzofuran, benzimidazole, indazole, benzoxazole, benzisooxazole, benzthiazole, benzisothiazole, purine, indoline, isoindoline.

45. (New) A method according to claim 37 wherein R_2 and R'_2 are joined to form cyclic structures selected from the group consisting of : pyrrolidine, piperidine, hexahydro-1H-azepine, morpholine or piperazine.

46. (New) A method according to claim 37 wherein Y_1 is selected from the group consisting of: croman, isochroman, benzofuran, cromene, 1,2,3,4-tetrahydronaphthalene, 1,4-dihydronaphthalene, indan, indene, benzopiperidine, indoline, isoindoline, quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline or pteridine, coumarin or 2,3-dihydrocoumarin.

47. (New) A method according to claim 37 wherein Y_2 is selected from the group consisting of: 9H-xanthone, 9H-xanthene, phenoxathiin, phenoxathiin-10-oxide, phenoxathiin-10-dioxide, acridine, phenazine, phenothiazine, phenoxazine, phenothiazine-5-oxide, phenothiazine-5-dioxide, thiathrene-5-dioxide, thiathrene-5-oxide, carbazole, dibenzo[b,d]furan, dibenzo[b,d]thiophene.

I. Explanation of amendments.

In this amendment, claims 1, 2, 4, 6, and 20-25 are amended, claims 11-15 and 26-31 are cancelled, and claims 32-47 are added. The specification is amended to correct a typographical error where, in a single instance, Y_3 is designated Y_1 and B16 Tyr is designated B12 Tyr. As Y_1 and Y_2 refer to bicyclic and tricyclic systems, respectively, one of ordinary skill in the art would recognize that the proviso "Y_1 cannot be an optionally substituted phenyl" must refer to Y_3 which may be defined as a phenyl or heteroaromatic ring. The correct designation of B16 Tyr finds support on page 27, lines 21-26. Claims 1, 2, 4, 6, and 20-25 as amended and new claims 32-47 find support throughout the application and are intended solely to correct these typographical errors or improve the style with which the invention is claimed in accordance with the Examiners suggestions. Applicant hereby states that the amendments and new claims do not represent new matter. The Applicants do not intend by these or any other amendments to abandon the subject matter of any claim as originally presented, and reserve the right to pursue such subject matter in other applications, such as continuing applications and divisional applications.

II. The Patent Office's allegation that the information disclosure statement failed to comply with the provisions of 37 CFR 1.97, 1.98, and MPEP 609 should be withdrawn.

New copies of the 94 references filed in the Information Disclosure Statement which were received by the Patent Office but not properly forwarded to the Examiner were sent again on March 31, 2003.

III. The Patent Office's rejection under 35 U.S.C. §112, second paragraph, has been rendered moot and should be withdrawn.

At pages 3-4 of the Office action, the Patent Office rejected claims 1, 2, 4, 6, and 20-31 under 35 U.S.C. § 112, second paragraph, alleging that these claims were indefinite. Claim 1 has been amended to recite a claim in accordance with the Examiner's suggestion.

Claims 2, 4, and 20-25 have been amended to recite proper Markush claim language in accordance with the Examiner's suggestion. Claim 6 was rejected for reciting "5 R1 groups". R1 is defined in lines 21-25 of claim 6 and per our discussion this term appears to be definite. Applicants submit that the claims are imbued with clarity and the rejection and in light of the above comments, request that the rejections based on 35 U.S.C. § 112, second paragraph should be withdrawn.

CONCLUSION

Withdrawal of the rejections and allowance all pending claims in the application are respectfully requested in view of the foregoing amendments and remarks.

An early allowance of all claims on the merits is respectfully requested. Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

Respectfully Submitted,

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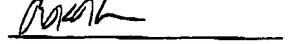
By: 
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May 12, 2003